Original Article

Cerebral Vasospasm in Critically Ill Patients with Aneurysmal Subarachnoid Hemorrhage: Does the Evidence Support the Ever-Growing List of Potential Pharmacotherapy Interventions?

Tyree H. Kiser, PharmD, FCCM, FCCP, BCPS*

Abstract

The occurrence of cerebral vasospasm after aneurysmal subarachnoid hemorrhage (SAH) is a significant event resulting in decreased cerebral blood flow and oxygen delivery. Prevention and treatment of cerebral vasospasm is vital to avert neurological damage and reduced functional outcomes. A variety of pharmacotherapy interventions for the prevention and treatment of cerebral vasospasm have been evaluated. Unfortunately, very few large randomized trials exist to date, making it difficult to make clear recommendations regarding the efficacy and safety of most pharmacologic interventions. Considerable debate exists regarding the efficacy and safety of hypervolemia, hemodilution, and hypertension (triple-H therapy), and the implementation of each component varies substantially amongst institutions. There is a new focus on euvolemic-induced hypertension as a potentially preferred mechanism of hemodynamic augmentation. Nimodipine is the one pharmacologic intervention that has demonstrated favorable effects on patient outcomes and should be routinely administered unless contraindications are present. Intravenous nicardipine may offer an alternative to oral nimodipine. The addition of high-dose magnesium or statin therapy has shown promise, but results of ongoing large prospective studies are needed before they can be routinely recommended. Tirilazad and clazosentan offer new pharmacologic mechanisms, but clinical outcome results from prospective randomized studies have largely been unfavorable. Locally administered pharmacotherapy provides a targeted approach to the treatment of cerebral vasospasm. However, the paucity of data makes it challenging to determine the most appropriate therapy and implementation strategy. Further studies are needed for most pharmacologic therapies to determine whether meaningful efficacy exists.

Key Words—cerebral vasospasm, intra-arterial, intrathecal, intraventricular, prevention, subarachnoid hemorrhage, treatment

Hosp Pharm 2014;49:923–941

INTRODUCTION

Aneurysmal subarachnoid hemorrhage (SAH) is a devastating neurologic condition that accounts for up to 5% of all cerebrovascular accidents and affects approximately 30,000 people each year in

the United States.¹⁻³ Patients who survive the initial cerebrovascular event are at high risk of further complications including rebleeding, cerebral vasospasm, and delayed cerebral ischemia. Rebleeding after SAH occurs in 5% to 10% of patients and is most likely

*Associate Professor, Department of Clinical Pharmacy, University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences, and Critical Care Pharmacy Specialist, University of Colorado Hospital, University of Colorado Anschutz Medical Campus, 12850 E. Montview Boulevard, C238, Aurora, CO 80045; phone: 303-724-2883; fax: 303-724-0979; e-mail: ty.kiser@ucdenver.edu

to occur in the first 72 hours after the initial hemorrhage.⁴ Early intervention utilizing coil embolization or microsurgical clip ligation reduces rebleeding risk.⁵

Cerebral vasospasm typically occurs between 3 and 14 days after SAH, with a peak incidence approximately 1 week after the original event. Vasospasm is described as intracranial artery narrowing caused by arterial vasoconstriction, vascular endothelium enlargement, or subendothelial fibrosis.⁶ A variety of mechanisms including inflammatory, immunologic, free radical production, and alterations in ion channels have been proposed to cause these deregulations in vessel constriction and relaxation. Release of vasoconstrictors, including serotonin and certain prostaglandins, from the platelets has been identified as a potential cause of early vasospasm.⁷ However, oxyhemoglobin release during erythrocyte lysis may be the primary culprit catalyzing these pro-vasospasm mechanisms.^{7,8} This pathophysiologic mechanism is supported by the observation that patients with thick blood in the ventricles or basal cistern (Fisher grading scale of 4) appear to be at the highest risk for cerebral vasospasm.⁹

The diagnosis of vasospasm is preferably determined by direct visualization on radiographic images, but it may also be assumed when alterations in cerebral blood flow velocities are observed via sonography.¹⁰ The occurrence of cerebral vasospasm is an important event, because it results in decreased cerebral blood flow and oxygen delivery that ultimately result in delayed cerebral ischemia or infarction. If the vasospasm persists and cannot be controlled, further neurological damage and reduced functional outcomes are likely to be observed.¹¹⁻¹³

Applying appropriate monitoring strategies to identify, prevent, or manage cerebral vasospasm is a critical component of treating patients with SAH. Frequent neurological assessment and determination of any new neurological deficits are the key methods for clinical identification of potential vasospasm and delayed cerebral ischemia. These repeated physiological assessments can also be supplemented with transcranial Doppler (TCD) ultrasonography. Not all events can be found on clinical examination. Digital subtraction angiography, computed tomography with angiography or perfusion imaging, or magnetic resonance imaging increase specificity. These radiological monitoring strategies should be used upon identification of any new alterations in consciousness, focal deficits, or alterations in cerebral blood flow velocities identified via TCD. The radiological monitoring is also particularly useful for asymptomatic patients or those who cannot participate in neurological assessments.

Radiological confirmation of cerebral vasospasm and/or delayed cerebral ischemia should trigger intervention.¹⁴ The purpose of this review is to evaluate the pharmacotherapy interventions for the prevention and treatment of cerebral vasospasm in patients with SAH.

LITERATURE REVIEW METHODOLOGY

The search strategy involved a review of the literature in MEDLINE (January 1966-December 2013) and EMBASE (1974-December 2013). Search terms utilized were subarachnoid hemorrhage, cerebral vasospasm, delayed cerebral ischemia, triple-H therapy, hypervolemia, hemodilution, hypertension, crystalloid, albumin, packed red blood cells, blood products, dopamine, phenylephrine, norepinephrine, vasopressin, dobutamine, milrinone, cilostazol, nimodipine, nicardipine, calcium channel blocker, magnesium, statin, endothelin antagonists, tirilazad, eicosapentaenoic acid, thrombolytic, and nitroprusside. All references that were included were selected based upon English language, human subjects, evaluation of scientific rigor, and relevance to recommendations within currently published guidelines¹⁵ or from the most recent Neurocritical Care Society's Multidisciplinary Consensus Conference.¹⁴ Preference was given to data generated from prospective randomized studies when available. Observational data, case reports, or case series were utilized when no other data were available. Nonpharmacologic interventions (eg, transluminal balloon angioplasty) and abstracts presented at scientific meetings were excluded. Unless otherwise specified, all pharmacotherapy interventions in the data discussed within this article were evaluated in addition to the usual standard of care at the investigator's institution.

PHARMACOTHERAPY INTERVENTIONS

Triple-H Therapy (Hypervolemia, Hemodilution, Hypertension)

Triple-H therapy refers to the combination of induced hypertension, hypervolemia, and hemodilution. Due to variations in implementation strategies, pharmacotherapy options, and goal endpoints within each of these components, the rationale and data supporting each of the triple-H components for both the prevention and treatment of cerebral vasospasm are discussed within separate sections below.

Volume Expansion Therapy

Rationale for volume expansion therapy. SAH patients are at risk for decreased circulating blood volume via

a variety of mechanisms including diuresis, negative nitrogen balance, decreased erythropoiesis, and iatrogenic blood loss.¹⁶ Hypovolemia appears to be a cumulative process, and decreased circulating blood volume is most prevalent in patients undergoing surgical intervention 6 to 72 hours post SAH.¹⁷

It has been postulated that because hypovolemia and fluid restriction are risk factors for cerebral vasospasm-induced delayed cerebral ischemia, prophylactic induction of hypervolemia should help alleviate this by increasing blood volume and cerebral blood flow. Hypervolemia created by volume expansion may prevent cerebral ischemia by increasing cardiac filling pressures and increasing cardiac output and blood pressure. Additionally, isotonic fluid administration may lower blood viscosity and decrease cerebrovascular resistance, thereby improving blood rheology.¹⁸

Hypervolemia versus normovolemia for prevention of cerebral vasospasm. Historically, hypervolemia was used frequently as both a preventative and a treatment method for cerebral vasospasm and delayed cerebral ischemia; however, data from the last decade have brought its prophylactic use into question. A prospective randomized study of 82 patients evaluated hypervolemia versus normovolemia fluid management that began the day after aneurysm clipping. All patients received dextrose 5% water with 0.9% sodium chloride at 80 mL/h for 14 days. The hypervolemic group patients received albumin 5% every 2 hours to achieve a target pulmonary artery diastolic pressure (PADP) of ≥ 14 mm Hg or a central venous pressure (CVP) of ≥ 8 mm Hg thereafter. Normovolemic patients received albumin 5% 250 mL every 2 hours to achieve a PADP of ≥ 7 mm Hg or CVP of ≥ 5 mm Hg. The results of the study demonstrated that cerebral blood flow was not improved with hypervolemia compared to normovolemia. Additionally, there were no differences in patients experiencing symptomatic vasospasm (8 patients in each group), patients requiring hypertensive therapy (6 patients normovolemia vs 7 patients hypervolemia), or functional independence post discharge (66% in each group). The authors concluded that induction of hypervolemia did not confer additional benefit over normovolemia in SAH patients.¹⁹

Similarly, a study of 32 patients compared triple-H therapy to normovolemic fluid therapy. In the normovolemic fluid group, patients received baseline infusions of 1,000 mL dextrose 5% water and 1,000 mL 0.9% sodium chloride every day until

day 12. Fluid management was targeted to maintain a neutral fluid balance. In the triple-H fluid management group, fluid management was titrated to achieve a CVP of 8 to 12 mm Hg, a hematocrit of 30% to 35%, and a mean arterial pressure (MAP) of more than 20 mm Hg greater than the preoperative MAP value. Patients received 2,000 mL of dextrose 5% water and 2,000 mL of 0.9% sodium chloride daily. Additionally, patients received 1,000 to 1,500 mL of albumin 4% until day 12. Dopamine 5 to 15 mcg/kg/min was administered to achieve MAP goals. A nonsignificant decrease in clinical symptoms of vasospasm was demonstrated in the triple-H group (31.5% vs 25%), but there was no difference in TCD identified vasospasm or functional outcomes between groups. Patients in the triple-H group had higher average daily costs and higher rates of congestive heart failure, which were attributed to the additional fluid therapy.²⁰

Even though the premise of hypervolemia therapy and the early positive findings within historical studies drove the routine utilization of this approach, the most recent data suggest that there is no benefit on cerebral blood flow or patient outcomes. There may actually be increased risk to the patient including increased incidence of bleeding, congestive heart failure, pulmonary edema, cerebral edema, and infections.^{21,22} Therefore, hypervolemia cannot be recommended for prophylaxis of cerebral vasospasm.²³

Hypervolemia for treatment of cerebral vasospasm. Although the prophylactic use of hypervolemia is no longer recommended, it is still frequently utilized for the treatment of cerebral vasospasm. Even in this setting, the efficacy and safety of hypervolemia as an individual component of triple-H therapy has to be reconsidered. Very few studies to date have evaluated the isolated effects of volume expansion on the reversal of vasospasm or its effects on intracranial pressure, cerebral blood flow, and brain tissue oxygenation. In a study of 6 euvolemic patients who developed clinical signs of vasospasm, administration of 0.9% sodium chloride 15 mL/kg over 1 hour was effective at improving cerebral blood flow and reducing cerebral ischemia.²⁴ This effect was demonstrated without any substantial effects on pulmonary artery occlusion pressure (PAOP), MAP, cardiac output, or CVP and was sustained for 2 to 3 hours. A study of 16 patients with severe vasospasm documented by angiography evaluated the efficacy of hypervolemia (mean 1,000 mL/day colloid plus 3,740 mL/day

crystalloid; mean CVP increase from 5.4 to 7.3 cm H₂O), phenylephrine-induced hypertension (mean MAP increase from 102 mm Hg to 132 mm Hg), or dobutamine-enhanced cardiac output (mean cardiac index increased from 4.1 to 6 L/min/m²) on cerebral blood flow. Contrary to the findings in the previously mentioned study, improvements in cerebral blood flow were only found in patients receiving phenylephrine or dobutamine.²⁵ Similarly, an observational study of 45 patients demonstrated that moderate hypertension increased brain tissue oxygenation in 90% of cases with a complication rate of 8% compared to hypervolemia, which was only effective in 12% of cases with a complication rate of 53%.²¹

The role of volume expansion as a single component of triple-H therapy for the treatment of cerebral vasospasm is supported by small studies demonstrating inconclusive results. Hypervolemia for the treatment of symptomatic vasospasm can be considered an initial treatment strategy in hypovolemic or euvolemic patients, but it is unlikely to benefit patients who are already volume replete (ie, CVP is already >8-10 mm Hg, PAOP >14-16 mm Hg).²⁶

Role of hypertonic saline in volume management. Although hypertonic saline is not considered a traditional component of triple-H therapy, it is commonly utilized for the reduction of intracranial pressure (ICP) and may have clinical benefits in certain SAH populations. Patients with poor clinical grade SAH who remain unresponsive after initial resuscitation generally have globally reduced cerebral blood flow and areas of severe vasospasm resulting in loss of autoregulation, raised ICP, and cerebral ischemia. A prospective study evaluated the effects of hypertonic saline in 44 patients with poor grade SAH. Patients were given a 2 mL/kg infusion of hypertonic saline 23.5% over 10 to 30 minutes. Administration of hypertonic saline increased arterial blood pressure, reduced intracranial pressure, and improved cerebral blood flow, brain tissue oxygenation, and brain tissue pH. The duration of effect for most parameters was between 2 and 4 hours.²⁷ Although the data are limited, hypertonic saline may provide a reasonable fluid alternative for patients with poor grade SAH and increased ICP.

Albumin versus crystalloids for volume expansion. The addition of albumin to 0.9% sodium chloride fluid management is a frequently employed strategy. Albumin is believed to be neuroprotective via several

potential mechanisms of action, including increasing serum oncotic pressure, increasing antioxidant and scavenger effects, improving microcirculatory blood flow, and reducing inflammatory response.²⁸ Studies of triple-H therapy frequently use albumin in their management; however, few studies have evaluated albumin compared to crystalloid monotherapy. An observational study of 140 patients demonstrated a trend toward reduced vasospasm (28% vs 19%; $P = .2$) and improved clinical outcomes at 3 months in patients who received albumin to maintain a CVP greater than 8 mm Hg. The same research group evaluated the safety and efficacy of escalating doses of albumin 25% in a recent pilot study of 47 adult subjects with SAH. All patients received 0.9% sodium chloride at 80 to 125 mL/h and maintained a goal CVP of 5 to 8 mm Hg. The albumin dosing strategies evaluated were albumin 0.625 g/kg, 1.25 g/kg, 1.875 g/kg, and 2.5 g/kg per day for up to 7 days. Doses up to 1.25 g/kg were generally well tolerated, but the study was stopped prematurely due to fluid overload resulting in pulmonary edema in 2 of the first 7 patients in the albumin 1.875 g/kg group.²⁹ Albumin is generally considered safe, but certain critically ill subpopulations (eg, trauma) have demonstrated worsening mortality when administered albumin.³⁰ A phase III study to evaluate the efficacy of albumin is currently underway and is needed prior to making any definitive conclusions about the use of albumin in SAH patients.

Blood products for volume management and oxygen delivery. Although in complete contrast to the hemodilution component of triple-H therapy, administration of blood products (mainly packed red blood cells [PRBC]) has been a strategy to increase intravascular volume and improve oxygen delivery to areas of brain ischemia. A prospective study of 35 consecutive patients with SAH or traumatic brain injury without cardiac disease measured local brain tissue oxygen partial pressure (PbtO₂) pre and post PRBC transfusion. A mean PbtO₂ increase of 15% occurred in 74% of patients with an average posttransfusion rise in hemoglobin of 1.4 ± 1.1 g/dL. In a prospective registry study of 611 patients, a higher hemoglobin nadir (9.9 ± 2.1 vs 8.6 ± 1.8 ; $P < .001$) and average daily hemoglobin value (11.7 ± 1.5 vs 10.9 ± 1.2 ; $P < .001$) was associated with greater functional independence at discharge (modified Rankin Scale, 0-3) and reduced risk of poor outcomes.³¹ A prospective

study of 44 patients with SAH and high risk for vasospasm randomized patients to a goal hemoglobin concentration of 10 g/dL or 11.5 g/dL. Patients with the goal Hgb of 11.5 g/dL received more PRBC (3 vs 2 units; $P = .045$). The number of cerebral infarctions on MRI (30% vs 41%), NIH Stroke Scale scores at 14 days (1 vs 2), and independence rate at 14 days (65% vs 44%) were numerically improved with the higher hemoglobin concentration; however, these results were not statistically significant.³² Based upon the current evidence, recommendations have been made to maintain a hemoglobin concentration of at least 8 to 10 g/dL, with some neurointensivists advocating for ≥ 10 g/dL in SAH patients with active cerebral ischemia.^{14,33} However, transfusion of PRBC is not without risks,³⁴ and a recent retrospective cohort study found that PRBC transfusion was independently associated with increased mortality in SAH patients (odds ratio [OR], 3.16; 95% CI, 1.02-9.69).³⁵

Hemodilution

Hemodilution reduces blood viscosity, reverses hypovolemia, increases cardiac output, and distends the vasospastic artery, ultimately improving blood flow through the vasospastic arterial vasculature. Hemodilution and reduced blood viscosity can be accomplished by either isovolemic or hypervolemic strategies. A prospective study of 8 patients evaluated the effects of isovolemic or hypervolemic hemodilution on cerebral blood flow. Isovolemic hemodilution on day 1 was accomplished by whole blood removal with simultaneous equal volume replacement with dextran 70% and albumin 4% to obtain a hematocrit value of 28%. On day 3, patients were transitioned to hypervolemic hemodilution through the autotransfusion of the blood withdrawn on day 1 plus equal parts of dextran and albumin (mean additional volume of 1.1 L). Regional cerebral blood flow was measured 60 minutes after each intervention. Isovolemic hemodilution caused modest increases in global cerebral blood flow; after hypervolemic hemodilution, cerebral blood flow returned to baseline. Additionally, the oxygen delivery capacity was reduced and hemodilution was not effective at reducing the area of brain ischemia.³⁶ Hemodilution appears to be effective at reducing blood viscosity and may improve cerebral blood flow; however, these effects may be countered by the reduced oxygen-carrying capacity of the hemodiluted blood. Therefore, intentional hemodilution cannot be routinely recommended for prophylaxis or treatment of cerebral vasospasm.

Hypertension

Patients with SAH often develop increased ICP due to the hemorrhage volume, increased cerebrospinal fluid outflow resistance, hydrocephalus, vasoparalysis, distal cerebral arteriolar vasodilation, and/or reactive hyperemia after hemorrhage. Consequential loss of cerebral autoregulation results in supraphysiologic cerebral perfusion pressure demands to maintain adequate perfusion of the brain. Administration of vasoactive agents can produce a sustained increase in arterial blood pressure, which results in improved cerebral perfusion pressure, cerebral blood flow, and brain tissue oxygenation.

Vasoactive agents are utilized to prevent and treat cerebral ischemia, a potential consequence of cerebral vasospasm, rather than to directly treat and reverse cerebral vasospasm. Prophylactic vasoactive medication therapy is generally used as necessary to maintain blood pressures required to prevent cerebral infarction, while attempting to minimize the risk of rebleeding. Treatment with vasoactive medications typically targets a higher systolic blood pressure or MAP goal, with dosages titrated to increase cerebral blood flow and reduce neurological deficits associated with vasospasm. For example, in a study of 58 patients with confirmed cerebral vasospasm after SAH, vasopressors (primarily dopamine) were used to induce arterial hypertension with a systolic blood pressure of up to 240 mm Hg in patients with secured aneurysms and up to 160 mm Hg in patients with unsecured aneurysms. Neurologic deterioration was reversed in 81% of patients, with sustained benefit in 74% of patients.³⁷ In a study of normovolemic patients, induction of hypertension to 25% to 50% above normal systolic arterial blood pressure resulted in neurological deficit improvement in 17 of 24 cases, indicating that hypertension may provide benefits without induced hypervolemia.³⁸

A variety of vasopressor options exist for the induction of hypertension; dopamine, phenylephrine, and norepinephrine are most commonly utilized in clinical practice. In a study of 13 SAH patients suspected of having clinical vasospasm and ischemia, dopamine administration (doses up to 20 mcg/kg/min) raised MAP from 90 ± 11 mm Hg to 111 ± 13 mm Hg. This increased cerebral blood flow in 54% of patients, placing them out of the ischemic range. Interestingly, reduced cerebral blood flow was identified in non-ischemic territories, which creates uncertainty about the ability to predict a universal response of cerebral blood flow to increased arterial pressures.³⁹ Norepinephrine targeted to achieve an increase in systolic

blood pressure of 20 to 60 mm Hg above symptomatic baseline, resulting in a systolic blood pressure of 140 to 190 mm Hg, was effective at reversing ischemic symptoms in a series of 7 patients with cerebral vasospasm.⁴⁰ In a safety study of 24 patients, 67% with cardiac disease, phenylephrine was utilized to increase MAP by 25%, with a further increase by 35% if no clinical improvement was observed. Neurological improvement occurred in 88% of patients. Phenylephrine did not result in reduced cardiac index measurements, and there were no occurrences of pulmonary edema or myocardial infarction.⁴¹ Arginine vasopressin (0.01-0.04 units/min) in addition to maximal phenylephrine therapy (4-5 mcg/kg/min) was evaluated in a group of 22 patients who were at very high risk for vasospasm or who were already exhibiting clinically symptomatic vasospasm. MAP was maintained at >100 mm Hg for prophylaxis and >110 mm Hg for symptomatic patients. Vasopressin was effective at allowing the reduction of phenylephrine dosage without reducing serum sodium concentrations or causing detrimental effects on vasospasm, ICP, or cerebral perfusion pressure.⁴²

Myocardial injury is not uncommon after SAH and is likely mediated by the release of catecholamines due to hypoperfusion. Inotropic agents improve cardiac output and therefore should increase cerebral blood flow; however, data regarding their effectiveness for cerebral vasospasm are mixed. The use of dobutamine to prophylactically elevate cardiac index by 25% compared to norepinephrine-induced hypertension (MAP > 100 mm Hg) failed to decrease the incidence of angiographic vasospasm in the first 14 days of treatment.⁴³ In a study of 23 patients with SAH who failed to respond to preload enhancement with fluids, the addition of dobutamine 5 to 10 mcg/kg/min was effective at reversing ischemic symptoms in 78% of patients.⁴⁴ A more recent study of 16 patients with cerebral vasospasm demonstrated that dobutamine enhancement of cardiac output alone, without changes in MAP, was effective at increasing cerebral blood flow.²⁵

Milrinone has both inotropic and vasodilatory effects and may provide an alternative with additional mechanistic benefits over dobutamine. Milrinone is a selective inhibitor of cyclic adenosine monophosphate-specific phosphodiesterase III, an important component of the cerebrovascular smooth muscle. It may also have anti-inflammatory effects mediated via inhibition of interleukins 1B and 6.⁴⁵ The addition of milrinone (0.1-0.2 mg/kg intravenous bolus, then 0.75-1.25 mcg/kg/min) to a standard of care protocol

for the treatment of patients with symptomatic vasospasm was found to be safe,⁴⁶ but comparative prospective studies are needed before conclusions can be made regarding its efficacy.

Comparative studies evaluating vasopressor options for the prevention and management of patients with cerebral vasospasm following SAH are unavailable. Therefore, dopamine, norepinephrine, or phenylephrine are all considered to be acceptable options and should be selected based on pharmacologic differences and desired patient-specific response. Arginine vasopressin, at a dose of 0.01 to 0.04 units/min, can be added as an additional vasopressor when primary vasopressor therapy has been maximized without achieving desired effects. Treatment of cerebral vasospasm via augmentation of cardiac index may be useful in patients with reduced cardiac output and hypervolemia; however, prophylactic utilization of inotropic agents to overdrive cardiac index as a mechanism of preventing cerebral vasospasm cannot be recommended at this time.

Summary of Triple-H Therapy Recommendations

Hypovolemia can occur in patients with SAH and should be avoided due to its association with worse clinical outcomes. In general, intravascular volume management should prophylactically target euolemia with utilization of an isotonic crystalloid as the preferred fluid for volume replacement.¹⁵ Hypervolemia with hypertension may have a role in treating cerebral vasospasm; however, the specific benefit of the hypervolemia component requires further evaluation. Addition of albumin and/or PRBC may be useful in certain patients, but more evidence is needed before definitive recommendations can be made. Intentional hemodilution to achieve a lower hemoglobin or hematocrit value and improve blood rheology should be avoided in most cases. Volume status should be routinely monitored and the use of CVP monitoring or a transpulmonary thermodilution system⁴⁷ in patients with central venous access may provide additional tools to assess a patient's volume status. A target CVP of ≥ 8 mm Hg has been utilized in many clinical studies; however, given the inability of CVP to reliably estimate intravascular volume, response to a CVP measurement should be interpreted on an individualized patient basis.¹⁴ Induced hypertension increases cerebral blood flow and cerebral perfusion pressure and is an effective method to treat delayed cerebral ischemia. Blood pressure targets can utilize predefined systolic or MAP goals or a percentage increase from baseline blood pressure

with further adjustments made based upon individual patient neurological response. In general, there is a revised recommendation for the use of euvolemic-induced hypertension rather than triple-H therapy as the initial method for treatment of most patients with cerebral vasospasm.^{15,22,48}

Calcium Channel Blockers

Calcium channel antagonists prevent calcium ion entry into smooth muscle cells during depolarization, causing inhibition of vasoconstriction. Cerebrovascular smooth muscle is more sensitive to changes in extracellular calcium concentrations than the systemic arterial smooth muscle. Moderate cerebral vasodilation has been demonstrated with the administration of calcium channel antagonists, and therefore it is considered the main mechanism for modulating the incidence and severity of cerebral vasospasm and delayed cerebral ischemia.^{49,50} Additionally, nimodipine may have other beneficial effects on patient outcomes that are independent of its ability to prevent cerebral vasospasm.⁵¹ Unfortunately, not all of the calcium channel antagonist effects are beneficial. Administration is associated with decreases in MAP and cerebral perfusion pressure (CPP), and recent data suggest that prevention of these decreases in MAP and CPP via the use of vasopressor therapy may be necessary to prevent decreased PbtO_2 and cerebral blood flow.⁵²

Nimodipine and nicardipine are the most well-studied calcium channel antagonists for the prevention of cerebral vasospasm and delayed cerebral ischemia. Sixteen studies, which included a total of 3,361 patients, were recently reviewed by the Cochrane Stroke Group (Figures 1 and 2).^{53,54} The combined results of the studies demonstrate that calcium channel antagonists reduce the risk of poor outcome (death or dependence), with those beneficial results being driven mostly by nimodipine.^{51,55-63}

The largest randomized multicenter double-blind placebo controlled study of nimodipine evaluated 554 patients with SAH. Within 96 hours of ictus, patients received nimodipine 60 mg orally every 4 hours for 21 days or placebo. The primary endpoint was incidence of cerebral infarction, ischemic neurological deficits, and outcome 3 months after study entry. Compared to placebo, nimodipine reduced cerebral infarction (22% vs 33%; $P = .003$) and poor outcomes (20% vs 33%; $P < .001$) and demonstrated a trend toward reduced rebleed rates (9% vs 14%; $P = .077$). The primary differences in outcome were a reduction in

death and disability in nimodipine-treated patients. Nimodipine was not without adverse effects. Nimodipine reduced both systolic (mean reduction of 7.1 mm Hg) and diastolic blood pressure (mean reduction of 3.6 mm Hg), but this did not result in increased heart rate, increased fluid administration, or decreased urine output. Additional adverse effects requiring discontinuation of nimodipine were rash (2 patients), cardiovascular effects (3 patients with headache, 1 with flushing, 1 with hypertension, and 1 with hypotension), and liver function abnormalities (4 patients).⁵⁵

Nicardipine may provide an intravenous alternative to nimodipine. The largest study of intravenous nicardipine to date was a multicenter prospective randomized placebo-controlled trial evaluating 906 patients with SAH. Patients were randomized from hospital days 0 to 7 to receive either high-dose intravenous nicardipine (0.15 mg/kg/h) or placebo for up to 14 days following SAH. The primary endpoint of the study was neurological recovery at 3 months following SAH, and it was not significantly different between nicardipine (55% with good recovery; mortality 17%) and placebo (56% with good recovery; mortality 18%). The incidence of symptomatic vasospasm was higher in placebo-treated patients compared to the nicardipine group (46% vs 32%; $P < .001$), and more patients in the placebo group required intentional hypervolemia, induced hypertension, and/or hemodilution administered to treat symptomatic vasospasm (38% vs 25%; $P < .001$). The most common adverse effect of nicardipine was hypotension, which occurred in 35% of patients; life-threatening hypotension occurred in only 3% of patients. Additional adverse effects were phlebitis (22.3%) and pulmonary edema in combination with azotemia (6%).⁶⁴ Due to these increased rates of adverse effects, a follow-up study randomized patients to 2 different doses of nicardipine to evaluate whether lower doses could be effective with improved safety outcomes. This multicenter prospective study randomized 365 SAH patients to high-dose (0.15 mg/kg/h) or lower dose (0.075 mg/kg/h) intravenous nicardipine for up to 14 days following SAH. Symptomatic vasospasm occurred in 31% of each group, and there were no differences in the percentage of good neurological outcomes (58% vs 59%) or mortality (11% vs 12%) at 3 months between the high-dose and lower dose treatment groups, respectively. Although there were no differences in clinical outcomes, lower dose nicardipine was better tolerated. Severe hypotension with evidence of end organ ischemia occurred in 1.1% of

Figure 1. Patient outcome according to type of calcium channel blocker administered and timing of outcome assessment. Reprinted, with permission, from Dorhout Mees SM, Rinkel GJ, Feigin VL, et al. Calcium antagonists for aneurysmal subarachnoid haemorrhage. *Cochrane Database Syst Rev.* 2007;CD000277. Copyright © 2007 John Wiley & Sons.

the high-dose group compared to 0.6% of the lower dose group. Pulmonary edema also occurred more frequently in the high-dose group compared to the low-dose group (34% vs 20%; $P < .01$).⁶⁵

Compared to other available pharmacotherapy interventions, nimodipine has currently demonstrated the best evidence for improved clinical outcomes in patients with SAH. Prophylactic oral nimodipine

therapy administered at 60 mg every 4 hours for 21 days after SAH hemorrhage is recommended for all SAH patients.^{14,15} If hypotension occurs, nimodipine can be administered as 30 mg every 2 hours.¹⁴ If decreases in MAP and CPP are not alleviated by adjusting the nimodipine dose and interval, then the administration of vasopressor therapy may be required to safely continue nimodipine therapy.

Figure 2. Patient outcomes in studies of magnesium in addition to nimodipine. Reprinted, with permission, from Dorhout Mees SM, Rinkel GJ, Feigin VL, et al. Calcium antagonists for aneurysmal subarachnoid haemorrhage. *Cochrane Database Syst Rev.* 2007;CD000277. Copyright © 2007 John Wiley & Sons.

Intravenous nicardipine may provide an alternative to nimodipine therapy in patients who cannot tolerate oral therapy or in patients in whom adequate absorption is questionable; however, the clinical outcome benefits with nicardipine have not been as reproducible as those demonstrated by nimodipine. Lower dose intravenous nicardipine (0.075 mg/kg/h) is equivalent to high-dose nicardipine and is better tolerated.

Magnesium

Hypomagnesemia occurs in more than 50% of patients with SAH and has been associated with poor outcomes.⁶⁶ Magnesium, a divalent cation, functions as a noncompetitive calcium antagonist via binding to voltage-dependent calcium channels. This action promotes vasodilation by inhibiting calcium entry into the cell, inhibiting vascular smooth muscle contraction, and decreasing glutamate release. Therefore, it may inhibit cerebral vasospasm and confer potentially neuroprotective effects similar to the dihydropyridine calcium channel antagonists.^{67,68}

Several clinical studies have evaluated the effects of magnesium on cerebral vasospasm and neurological outcomes in patients with SAH.⁶⁹⁻⁷⁵ A recent multicenter phase III randomized placebo-controlled study enrolled 327 patients with SAH within 48 hours of hemorrhage onset. The primary outcome was a favorable neurological outcome at 6 months. Patients were randomized to receive magnesium 20 mmol (5 g) over 30 minutes followed by a continuous infusion of 80 mmol (20 g) per day for up to 14 days after hemorrhage or placebo (0.9% sodium chloride). The magnesium infusion was adjusted to achieve a magnesium concentration twice the patient's baseline value up to a maximum of 2.5 mmol/L. The percentage of patients with favorable

outcome at 6 months was similar in the magnesium (64%) and placebo (63%) groups. The percentage of patients with clinical vasospasm was also similar in the magnesium (25%) and placebo (18%) groups. Magnesium infusions were discontinued in 3 patients because of severe limb weakness, refractory hypernatremia, and severe hypocalcaemia. There were no differences in the rates of hypotension, cardiac failure, acute renal failure, pneumonia, sepsis, pulmonary embolism, myocardial infarctions, or gastrointestinal bleeding between the treatment groups.⁷³ A recent meta-analysis of 6 studies (875 patients) receiving intravenous magnesium demonstrated a nonsignificant decrease in delayed cerebral ischemia (relative risk [RR], 0.87; 95% CI, 0.36-2.09; $P = .75$) and decreased delayed cerebral infarction rate (RR, 0.58; 95% CI, 0.35-0.97; $P = .04$). The pooled relative risk for a favorable outcome at 3 months was 1.14 (95% CI, 0.99-1.31; $P = .07$).⁷²

Despite animal and phase II data showing promising results with intravenous magnesium, the most recent phase III data regarding clinical efficacy has failed to demonstrate a clear benefit of magnesium therapy in patients with SAH. It is possible that the lack of benefit is due to poor penetration of magnesium into the cerebrospinal fluid. The regimen used in the phase III clinical study was only able to increase cerebrospinal fluid magnesium concentrations from 11% to 21% of the plasma. Even though magnesium is a relatively cheap and safe medication, it cannot be routinely recommended at this time. Rather than aggressive magnesium therapy, the current recommendation is to administer magnesium as necessary to prevent hypomagnesemia.¹⁴ Results of a planned second phase III study should help elucidate any potential benefits of magnesium in SAH.

HMG-CoA Reductase Inhibitors (Statins)

The potential therapeutic benefits of statins have been tested in a variety of disease states, including cerebral vasospasm post SAH. Statins upregulate endothelial nitric oxide synthase and the availability of endogenous nitric oxide by inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase. This corrects the imbalance between the nitric oxide and endothelin pathways, which is believed to be a main contributor to the pathophysiology of cerebral vasospasm.⁷⁶ Additionally, statins may decrease glutamate-mediated excitotoxicity, reduce production of reactive oxygen species, and modulate the inflammatory response via alterations in the cytokine response.^{77,78}

Several prospective studies have evaluated the effects of statins (simvastatin, pravastatin, or atorvastatin) on vasospasm and delayed cerebral ischemia with mixed results.⁷⁹⁻⁸⁵ A phase II randomized placebo-controlled trial of 80 SAH patients placed patients on pravastatin 40 mg daily or placebo within 72 hours of hemorrhage and continued therapy for up to 14 days. Vasospasm and severe vasospasm were decreased by 32% ($P = .006$) and 42% ($P = .044$), respectively, in pravastatin-treated patients. Pravastatin also decreased the incidence of vasospasm-delayed cerebral ischemia by 83% ($P < .001$) and mortality by 75% ($P = .037$). The duration of severe vasospasm was shortened by 0.8 days in the pravastatin group. Unfortunately, these impressive results have not been reproduced in more recent studies.

A phase II randomized, double-blind, placebo-controlled study of 39 statin-naïve SAH patients evaluated simvastatin 80 mg daily or placebo administered within 96 hours of hemorrhage. Therapy was continued until discharge from the intensive care unit or a maximum of 21 days. Angiographically confirmed vasospasm occurred in 26% of simvastatin and 40% of placebo patients. Vasospasm-related ischemic infarcts occurring in 11% of simvastatin and 25% of placebo patients, but these differences were nonsignificant. Simvastatin therapy required discontinuation in 1 patient due to increased alanine aminotransferase and aspartate aminotransferase levels. Enthusiasm for statin therapy was further stymied when a similar study of simvastatin utilizing comparable methodology and size was unable to demonstrate any difference in outcomes.⁸³

A more recent study of atorvastatin evaluated whether statin therapy reduced vasospasm-induced ischemia by utilizing daily measurements of serum S100B, a biomarker for cerebral ischemia. Computed tomography was used to measure the ischemic lesion

volume. Atorvastatin 40 mg once daily was administered to 142 patients for 21 days. These patients were compared to a historical control of 136 patients who were not managed with statin therapy. Atorvastatin treatment reduced the incidence of cerebral vasospasm, severity of vasospasm, volume of ischemia, and serum S100B levels, but there were no differences in rescue therapy requirements or clinical outcomes at 1 year.⁸⁴

The addition of statin therapy in statin-naïve patients with SAH appears safe and has demonstrated clinical benefits in most of the clinical studies to date. Completion of the ongoing Simvastatin in Aneurysmal Subarachnoid Haemorrhage (STASH) study (<http://www.stashtrial.com/home.html>) should provide more definitive evidence to guide recommendations for routine use of statins in SAH. In the interim, if a decision is made to initiate statin therapy, statins therapy should be started within 96 hours (preferably 48 hours) post ictus and continued for 14 to 21 days. Given the aggressiveness of statin dosing utilized in most studies, liver function and creatinine phosphokinase should be monitored periodically throughout treatment to avoid the potential of rare, but clinically significant, hepatotoxicity or rhabdomyolysis. Due to worsened outcomes seen after discontinuation of statin therapy in patients with ischemic stroke or myocardial infarction, statin therapy should be continued in SAH patients who were receiving these medications prior to admission.¹⁴

Endothelin Receptor Antagonists

Endothelin receptor antagonists inhibit the binding of the potent vasoconstrictor, endothelin-1, to its receptors on vascular smooth muscle cells. Clazosentan, as selective endothelin-1 receptor antagonist, has been the most well studied to date.⁸⁶⁻⁹⁰ An early phase II study of clazosentan (CONSCIOUS-1) demonstrated that clazosentan produced dose-dependent reductions in angiographic vasospasm, with a 65% relative risk reduction at the highest dose of 15 mg/h.⁸⁶ Based upon these results, 2 phase III studies were conducted to evaluate clazosentan 5 mg/h or 15 mg/h compared to placebo (CONSCIOUS-2 and CONSCIOUS-3).^{87,90} The primary outcome evaluated was a composite of all-cause mortality, vasospasm-related new cerebral infarcts, delayed ischemic neurological deficit due to vasospasm, and rescue therapy for vasospasm. In the CONSCIOUS-2 study, 768 patients were randomized to clazosentan 5 mg/h and 389 patients received placebo for up to 14 days. The composite endpoint occurred less frequently in the clazosentan group (21%) compared to the placebo

group (25%), however this difference was not significant ($P = .1$). The difference between groups was driven by a reduced need for rescue therapy for cerebral vasospasm with clazosentan. Interestingly, poor functional outcomes (Glasgow Outcome Scale ≤ 4) occurred more frequently in the clazosentan-treated patients (29% vs 25%, respectively; $P = .1$) and mortality between groups was the same. Clazosentan adverse events requiring discontinuation of the study drug were pulmonary edema, hypotension, cerebrovascular spasm, pleural effusion, and cerebral infarction. Of the adverse events reported, lung complications, anemia, and hypotension were more common with clazosentan than placebo.⁸⁷ Based upon the results of this study, CONSCIOUS-3 was stopped early after enrolling only 577 of its planned 1,500 patients. The results of CONSCIOUS-3 demonstrated similar findings to CONSCIOUS-2 for the 5 mg/h clazosentan dose. The clazosentan 15 mg/h dose was effective for reducing vasospasm-related morbidity, but it did not improve functional outcomes (Glasgow Outcome Scale ≤ 4 occurred in 24% of placebo vs 28% of clazosentan 15 mg/h, respectively; $P = .266$).

Results from studies of clazosentan to date demonstrate that it is effective at reducing cerebral vasospasm in patients with SAH. Unfortunately, this benefit does not translate into improved patient outcomes. Additionally, adverse events including anemia, pulmonary complications, and hypotension are more common in clazosentan patients. Therefore, the use of endothelin receptor antagonists for patients with SAH cannot be recommended at this time.

Tirilazad

Tirilazad is a non-glucocorticoid 21-aminosteroid that functions as a free radical scavenger by inhibiting lipid peroxidation. This antioxidant effect is believed to confer neuroprotective benefits. Interest in tirilazad for cerebral vasospasm was founded after a secondary reduction in angiographic vasospasm, via an unknown mechanism, was observed during a phase II clinical study.⁹¹ After this initial study, 4 randomized controlled studies were conducted to evaluate the efficacy and safety of tirilazad in patients with SAH.⁹²⁻⁹⁵ These studies demonstrate discordant results regarding tirilazad's effects on neurological outcomes, incidence of cerebral vasospasm, and benefits in men versus women. A recent meta-analysis of these studies, including a total of 3,797 patients, concluded that tirilazad does not decrease unfavorable clinical outcomes (per the Glasgow Outcome Scale) (OR, 1.04; 95% CI, 0.89-1.2) or reduce cerebral

infarction rates (OR, 1.04; 95% CI, 0.89-1.22). However, a reduction in symptomatic vasospasm was observed in patients receiving tirilazad (OR, 0.8; 95% CI, 0.69-0.93). The most common adverse event of tirilazad reported was phlebitis.

A dissociation between tirilazad's effects on cerebral vasospasm and neurological outcomes currently exists. Even though tirilazad appears to be a relatively safe medication, the lack of significant benefit on clinical outcomes makes the use of this agent costly and economically unsound.⁹⁶ Therefore, its use cannot be recommended.

Cilostazol

Cilostazol, a selective inhibitor of phosphodiesterase 3, may attenuate cerebral vasospasm by increasing intracellular concentrations of cAMP, resulting in vasodilatory effects and inhibition of platelet aggregation. A recent prospective study randomly assigned patients treated by clipping within 72 hours from the onset of SAH to cilostazol 100 mg twice daily ($n = 54$) or usual therapy ($n = 55$). Symptomatic vasospasm was reduced to 13% in the cilostazol group compared to 40% in the usual care group ($P = .002$). Angiographic vasospasm was lower in the cilostazol group than in the usual care group (50% vs 77%; $P = .006$). The number of new cerebral infarctions was also lower in the cilostazol group (11% vs 29%; $P = .03$). However, no differences were demonstrated in clinical outcomes at 1, 3, or 6 months or the length of hospitalization between the groups.⁹⁷ Despite preliminary results demonstrating potential efficacy for cerebral vasospasm and overall benign safety profile, additional studies are needed before routine use of cilostazol can be recommended.

Eicosapentaenoic Acid

Rho-kinase activation and sphingosylphosphorylcholine (SPC) concentrations are elevated in patients with SAH and may play a role in the pathogenesis of cerebral vasospasm. Eicosapentaenoic acid (EPA) is an omega-3 polyunsaturated fatty acid that has been evaluated for a variety of indications due to its potential pleiotropic effects. EPA inhibits SPC-Rho-kinase-activated Ca^{2+} -sensitization of the vascular smooth muscle. This inhibits vascular smooth muscle contraction and is the proposed mechanism for reducing vasospasm in patients with SAH.⁹⁸ A recent open-label prospective study evaluated EPA to no EPA in 162 patients with SAH. EPA patients received 900 mg of EPA ethyl ester 3 times daily starting after surgical clipping and continued

therapy for 30 days. The occurrence of symptomatic vasospasm (15% vs 30%; $P = .02$) and cerebral infarction caused by cerebral vasospasm (7% vs 21%; $P = .01$) were lower in patients receiving EPA. The percentage of patients with a favorable outcome did not differ between the 2 groups at day 30 or day 180. Diarrhea, epigastric discomfort, and nausea were the only EPA-related adverse effects reported.⁹⁹ Although these data appear promising, prospective randomized studies are needed before any conclusions can be made regarding the utility of EPA for prevention of cerebral vasospasm in SAH patients.

Locally Administered Pharmacotherapy

Intra-arterial, intrathecal, or intraventricular administration of medications provides a targeted approach to the treatment of cerebral vasospasm. Direct administration to the site of action should result in high tissue concentrations and increased efficacy, particularly for small vessel vasospasm. However, most evidence of locally administered pharmacotherapy is based upon case series, and little is known about the pharmacokinetics and pharmacodynamics of the administered medications.¹⁰⁰ Therefore, it is difficult to determine the most appropriate medication dose or frequency of administration, and clinical application is generally accomplished by mimicking successful case reports published within the available literature.

Papaverine

Papaverine preferentially vasodilates the vascular smooth muscle of cerebral and coronary arteries by inhibiting cyclic adenosine monophosphate and cyclic guanosine 3,5 monophosphate phosphodiesterase activity. Intra-arterial administration of papaverine (doses ranging from 150-600 mg) has demonstrated good success in the treatment of cerebral vasospasm in most reported clinical experiences.¹⁰¹⁻¹¹¹ The administration technique has varied, but most studies either utilized a bolus over 60 seconds or a slow infusion of 0.1% to 0.6% solution at 1 to 7 mL/min. Papaverine administration is not without adverse events. The most noteworthy events reported include hemiplegia and seizures, but increased ICP, agitation, altered mental status, and hypotension have also been observed.¹¹² High exposure to papaverine may cause neurotoxicity due to altered mitochondrial cellular respiration.¹¹³ Given the potential for adverse events and the availability of alternative intra-arterial options, papaverine cannot be routinely recommended for the treatment of vasospasm.

Calcium Channel Blockers

Nicardipine. Nicardipine manufactured for intravenous injection can be administered by intra-arterial,¹¹⁴⁻¹¹⁶ intrathecal,¹¹⁷ or intraventricular¹¹⁸ routes for the treatment of cerebral vasospasm. Intra-arterial nicardipine was evaluated in a prospective study of 18 patients and a total of 44 vessels. Intravenous nicardipine was diluted with 0.9% sodium chloride to a concentration of 0.1 mg/mL and administered in 1 mL aliquots through a microcatheter to a maximum dose of 5 mg per vessel. Nicardipine was effective at inducing vasodilation of all vessels evaluated, and mean peak systolic velocities on TCD were reduced from pretreatment values for 4 days after infusion. Neurologic improvement was seen in 42% of patients. Increases in ICP were observed in 5 patients.¹¹⁴

In a prospective case series of 6 patients, nicardipine 4 mg every 12 hours was administered intrathecally. Ventricular drains were clamped for 30 minutes following administration. Evaluation of middle cerebral artery velocity via TCD demonstrated that nicardipine had positive effects on cerebral arterial flow.¹¹⁷ In a retrospective case series of 8 patients, intraventricular nicardipine 4 mg was administered every 12 hours for a total of 5 to 17 days. The drug was well tolerated, and 7 of the 8 patients had moderate to good functional outcomes.¹¹⁸

A potential novel option for administering nicardipine is the insertion of nicardipine-releasing implants at the time of surgical intervention. A phase II prospective, randomized, double-blind evaluation of nicardipine prolonged release implants in 32 patients demonstrated that nicardipine was more effective than placebo at reducing the incidence of vasospasm (7% vs 73%; $P < .05$) and delayed cerebral ischemia (14% vs 47%; $P < .05$).¹¹⁹

Although relatively little data are available on the use of locally administered nicardipine therapy, it appears to provide effective and sustained effects on the cerebral vasculature. Additionally, nicardipine appears to be associated with fewer adverse events when compared to other locally administered vasodilatory therapies.

Verapamil. Verapamil is a benzylalkylamine calcium channel antagonist that reduces the influx of calcium through L-type calcium channels in smooth muscle cells. Due to its effectiveness in treating coronary vasospasm, intra-arterial verapamil has been utilized in the management of cerebral vasospasm.¹²⁰⁻¹²² Data evaluating the use of intra-arterial verapamil are mostly

limited to retrospective evaluations of clinical practice. In a retrospective evaluation of 12 patients with refractory vasospasm, high-dose verapamil was administered into 36 vessels at a dosage of between 25 and 360 mg (total dose per treatment of 70-720 mg) per vessel. Verapamil infusions were administered over 1 to 20.5 hours. Verapamil was effective at reversing vasospasm in 32 vessels, and 9 of the 12 patients treated had no new evidence of ischemia on computed tomography.¹²⁰ Verapamil appears to be effective at reversing cerebral vasospasm. ICP, heart rate, and blood pressure should be monitored during administration to limit adverse effects.¹²³

Nitroprusside

Sodium nitroprusside causes vasodilation of the vascular smooth muscle via release of nitric oxide. Intraventricular administration of nitroprusside was evaluated in a prospective study of 25 SAH patients with severe vasospasm refractory to conventional therapy. Nitroprusside 4 mg/mL was administered intraventricularly via an Ommaya reservoir in escalating dosages and frequency depending on the patient's tolerance and fall in mean flow velocity on TCD. The mean nitroprusside dose administered was 18.4 mg (range, 8-30 mg). An improvement in mean flow velocity was seen in all patients. Adverse effects related to nitroprusside in these patients were hypotension and vomiting.¹²⁴

Milrinone

Milrinone is a bipyridine inotropic vasodilator that selectively inhibits peak III cyclic adenosine monophosphate phosphodiesterase isozyme found in cardiac and vascular muscle. This activity causes increases of intracellular ionized calcium, contractile force in heart muscles, and vasodilation. Intra-arterial milrinone has been evaluated for the treatment of cerebral vasospasm.¹²⁵⁻¹²⁷ A prospective study of 22 patients evaluated the effectiveness of intra-arterial milrinone (8 mg over 30 minutes, repeated up to a maximum of 24 mg as needed) combined with intravenous milrinone 0.5 to 1.5 mcg/kg/min for treating angiographically proven cerebral vasospasm. Intra-arterial milrinone resulted in a mean increase in arterial diameter of 53% and was effective at reversing cerebral vasospasm. The most common adverse effect related to milrinone was increased heart rate, and 5 patients had vasospasm recurrence within 48 hours post intra-arterial administration.

Cisternal irrigation of milrinone has also been evaluated. In a study of 12 patients, lactated Ringer solution containing urokinase (120 IU/mL), ascorbic acid (3.5 mg/mL), and milrinone (3.6 mcg/mL) was continuously infused at 30 mL/h for up to 2 weeks. In this study, only 3 of the 12 patients developed symptomatic cerebral vasospasm, with 1 patient suffering a permanent neurological deficit.¹²⁸

Thrombolytics

Locally administered intrathecal thrombolytics enhance the conversion of plasminogen to plasmin by binding to fibrin, initiating fibrinolysis. This action can speed the clearance rate of blood from the basal cisterns and ventricles and may reduce the incidence of cerebral vasospasm and complications associated with SAH.

Urokinase and alteplase are the most well-studied thrombolytics in patients with SAH, but the dosages and administration frequencies that were evaluated vary substantially.¹²⁹⁻¹³⁶ Urokinase dosages of 6,000 to 120,000 IU daily and durations of 1 to 12 days have been utilized. Similarly, alteplase dosages from 1 to 10 mg have been utilized with variable durations. More recently, administration of alteplase at dosages of 1 to 3 mg (followed by clamping the external ventricular drain for 1 hour) twice daily until nearly complete clearance of blood from the third/fourth ventricles has been suggested.¹³⁴ A meta-analysis of 5 randomized controlled trials (total of 465 patients) concluded that administration of intrathecal thrombolytics reduced poor outcomes (OR, 0.52; 95% CI, 0.34-0.78; $P < .01$) and delayed neurologic deficits (OR, 0.54; 95% CI, 0.34-0.87; $P = .01$), angiographic vasospasm (OR, 0.32; 95% CI, 0.15-0.70; $P < .01$), and chronic hydrocephalus (OR, 0.33; 95% CI, 0.15-0.74; $P < .01$) without increasing hemorrhagic and infectious complications.¹³³ Intrathecal thrombolytics are not without risk, and exacerbations of perihematomal edema and sterile meningitis have occurred.¹³⁴ Despite the potential for improved outcomes with intrathecal thrombolytic administration, routine administration is not currently recommended.^{14,77,137}

CONCLUSION

Cerebral vasospasm significantly increases morbidity and mortality after SAH. Clinical studies have tested a variety of pharmacotherapy interventions for the prevention and treatment of cerebral vasospasm. Unfortunately, the majority of these studies are not large randomized trials, making it difficult to construct clear recommendations regarding the efficacy and safety of most pharmacologic interventions.

Euvolemia is recommended over hypervolemia as a preventative method for cerebral vasospasm. Prophylactic hemodilution or administration of blood products to maintain a specific target hemoglobin/hematocrit concentration cannot be routinely recommended. Initiation of triple-H therapy may provide a reasonable approach to the treatment of cerebral vasospasm and delayed cerebral ischemia. However, considerable debate still exists regarding which of the 3 components (hypervolemia, hemodilution, or hypertension) should be routinely employed. Therefore, practice patterns at individual institutions still vary substantially. Hypertension remains the most steadfast component of triple-H therapy for improving cerebral perfusion and oxygenation, thus current guidelines recommend a euvolemic-induced hypertension model.¹⁵ Triple-H therapy is not without risks, and patients should be closely monitored for signs of cardiac failure, pulmonary and cerebral edema, electrolyte abnormalities, and rupture of unsecured aneurysms. Recent evidence suggests that euvolemic fluid management with induction of hypertension may provide the preferred initial approach to treatment of patients with cerebral vasospasm and delayed cerebral ischemia.

Nimodipine is the one pharmacologic intervention that has most consistently demonstrated beneficial effects on patient outcomes in prospective studies and should be routinely employed for patients with SAH. Intravenous nicardipine has demonstrated the ability to reduce the incidence of cerebral vasospasm and offers an alternative to oral nimodipine; however, it has yet to demonstrate clear improvements in clinical outcomes. Inducing hypermagnesemia with the administration of high doses of intravenous magnesium demonstrated benefits in smaller pilot studies; however, given the equivocal results of a recent large randomized trial, routine use of this agent cannot be recommended. Standard of care magnesium supplementation should be utilized as necessary to avoid hypomagnesemia in patients with SAH. It is recommended that patients who are on statin therapy prior to admission continue statin therapy. Results of ongoing large prospective studies are required before a recommendation can be made to routinely add statin therapy in statin-naïve patients with SAH. Locally administered pharmacotherapy provides a targeted approach to the treatment of cerebral vasospasm. However, most evidence to date consists of case series, and therefore it is difficult to determine the most appropriate therapy and implementation strategy. Of the currently available agents evaluated for local administration, nicardipine and thrombolytics appear to be the most intriguing.

SAH is a multifaceted disease, and most patients require surgical and pharmacologic intervention to improve neurological outcomes. Given the complexity of SAH disease and the multitude of treatment options for the prevention and treatment of cerebral vasospasm and delayed cerebral ischemia, the efforts of a multidisciplinary health care team are critical. This approach allows for individualized patient therapy and increases the likelihood that pharmacologic interventions and monitoring strategies are based on the best available evidence, ultimately increasing the probability of optimal patient outcomes.

ACKNOWLEDGMENTS

The author reports no conflicts of interest.

REFERENCES

1. Sudlow CL, Warlow CP. Comparable studies of the incidence of stroke and its pathological types: Results from an international collaboration. International Stroke Incidence Collaboration. *Stroke*. 1997;28:491-499.
2. Linn FH, Rinkel GJ, Algra A, van Gijn J. Incidence of subarachnoid hemorrhage: Role of region, year, and rate of computed tomography: A meta-analysis. *Stroke*. 1996;27:625-629.
3. Shea AM, Reed SD, Curtis LH, Alexander MJ, Villani JJ, Schulman KA. Characteristics of nontraumatic subarachnoid hemorrhage in the United States in 2003. *Neurosurgery*. 2007;61:1131-1137; discussion 7-8.
4. Fujii Y, Takeuchi S, Sasaki O, Minakawa T, Koike T, Tanaka R. Ultra-early rebleeding in spontaneous subarachnoid hemorrhage. *J Neurosurg*. 1996;84:35-42.
5. Molyneux AJ, Kerr RS, Yu LM, et al. International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: A randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion. *Lancet*. 2005;366:809-817.
6. Hughes JT, Schianchi PM. Cerebral artery spasm. A histological study at necropsy of the blood vessels in cases of subarachnoid hemorrhage. *J Neurosurg*. 1978;48:515-525.
7. Osaka K. Prolonged vasospasm produced by the breakdown products of erythrocytes. *J Neurosurg*. 1977;47:403-411.
8. Liu-Deryke X, Rhoney DH. Cerebral vasospasm after aneurysmal subarachnoid hemorrhage: An overview of pharmacologic management. *Pharmacotherapy*. 2006;26:182-203.
9. Claassen J, Carhuapoma JR, Kreiter KT, Du EY, Connolly ES, Mayer SA. Global cerebral edema after subarachnoid hemorrhage: Frequency, predictors, and impact on outcome. *Stroke*. 2002;33:1225-1232.
10. Vergouwen MD, Vermeulen M, van Gijn J, et al. Definition of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage as an outcome event in clinical trials and

observational studies: Proposal of a multidisciplinary research group. *Stroke*. 2010;41:2391-2395.

11. Fisher CM, Roberson GH, Ojemann RG. Cerebral vasospasm with ruptured saccular aneurysm—the clinical manifestations. *Neurosurgery*. 1977;1:245-248.
12. Fergusen S, Macdonald RL. Predictors of cerebral infarction in patients with aneurysmal subarachnoid hemorrhage. *Neurosurgery*. 2007;60:658-667; discussion 67.
13. Vergouwen MD, Ilodigwe D, Macdonald RL. Cerebral infarction after subarachnoid hemorrhage contributes to poor outcome by vasospasm-dependent and -independent effects. *Stroke*. 2011;42:924-929.
14. Diringer MN, Bleck TP, Hemphill JC 3rd, et al. Critical care management of patients following aneurysmal subarachnoid hemorrhage: Recommendations from the Neurocritical Care Society's Multidisciplinary Consensus Conference. *Neurocrit Care*. 2011;15:211-240.
15. Connolly ES, Jr., Rabinstein AA, Carhuapoma JR, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2012;43:1711-1737.
16. Maroon JC, Nelson PB. Hypovolemia in patients with subarachnoid hemorrhage: Therapeutic implications. *Neurosurgery*. 1979;4:223-226.
17. Nakagawa A, Su CC, Sato K, Shirane R. Evaluation of changes in circulating blood volume during acute and very acute stages of subarachnoid hemorrhage: Implications for the management of hypovolemia. *J Neurosurg*. 2002;97:268-271.
18. Mori K, Arai H, Nakajima K, Tajima A, Maeda M. Hemorheological and hemodynamic analysis of hypervolemic hemodilution therapy for cerebral vasospasm after aneurysmal subarachnoid hemorrhage. *Stroke*. 1995;26:1620-1626.
19. Lennihan L, Mayer SA, Fink ME, et al. Effect of hypervolemic therapy on cerebral blood flow after subarachnoid hemorrhage: A randomized controlled trial. *Stroke*. 2000;31:383-391.
20. Egge A, Waterloo K, Sjöholm H, Solberg T, Ingebrigtsen T, Romner B. Prophylactic hyperdynamic postoperative fluid therapy after aneurysmal subarachnoid hemorrhage: A clinical, prospective, randomized, controlled study. *Neurosurgery*. 2001;49:593-605; discussion 6.
21. Raabe A, Beck J, Keller M, Vatter H, Zimmermann M, Seifert V. Relative importance of hypertension compared with hypervolemia for increasing cerebral oxygenation in patients with cerebral vasospasm after subarachnoid hemorrhage. *J Neurosurg*. 2005;103:974-981.
22. Dankbaar JW, Slooter AJ, Rinkel GJ, Schaaf IC. Effect of different components of triple-H therapy on cerebral perfusion in patients with aneurysmal subarachnoid haemorrhage: A systematic review. *Crit Care*. 2010;14:R23.
23. Treggiari MM. Hemodynamic management of subarachnoid hemorrhage. *Neurocrit Care*. 2011;15:329-335.
24. Jost SC, Diringer MN, Zazulia AR, et al. Effect of normal saline bolus on cerebral blood flow in regions with low baseline flow in patients with vasospasm following subarachnoid hemorrhage. *J Neurosurg*. 2005;103:25-30.
25. Joseph M, Ziadi S, Nates J, Dannenbaum M, Malkoff M. Increases in cardiac output can reverse flow deficits from vasospasm independent of blood pressure: A study using xenon computed tomographic measurement of cerebral blood flow. *Neurosurgery*. 2003;53:1044-1051; discussion 51-52.
26. Findlay JM. The present role of "triple-H" therapy in the management of cerebral vasospasm. *World Neurosurg*. 2010;74:244-246.
27. Al-Rawi PG, Tseng MY, Richards HK, et al. Hypertonic saline in patients with poor-grade subarachnoid hemorrhage improves cerebral blood flow, brain tissue oxygen, and pH. *Stroke*. 2010;41:122-128.
28. Horstick G, Lauterbach M, Kempf T, et al. Early albumin infusion improves global and local hemodynamics and reduces inflammatory response in hemorrhagic shock. *Crit Care Med*. 2002;30:851-855.
29. Suarez JI, Martin RH, Calvillo E, et al. The Albumin in Subarachnoid Hemorrhage (ALISAH) multicenter pilot clinical trial: Safety and neurologic outcomes. *Stroke*. 2012;43:683-690.
30. Myburgh J, Cooper DJ, Finfer S, et al. Saline or albumin for fluid resuscitation in patients with traumatic brain injury. *N Engl J Med*. 2007;357:874-884.
31. Naidech AM, Jovanovic B, Wartenberg KE, et al. Higher hemoglobin is associated with improved outcome after subarachnoid hemorrhage. *Crit Care Med*. 2007;35:2383-2389.
32. Naidech AM, Shaibani A, Garg RK, et al. Prospective, randomized trial of higher goal hemoglobin after subarachnoid hemorrhage. *Neurocrit Care*. 2010;13:313-320.
33. Kramer AH, Diringer MN, Suarez JI, Naidech AM, Macdonald LR, Le Roux PD. Red blood cell transfusion in patients with subarachnoid hemorrhage: A multidisciplinary North American survey. *Crit Care*. 2011;15:R30.
34. Hebert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med*. 1999;340:409-417.
35. Festic E, Rabinstein AA, Freeman WD, et al. Blood transfusion is an important predictor of hospital mortality among patients with aneurysmal subarachnoid hemorrhage. *Neurocrit Care*. 2013;18(2):209-15.
36. Ekelund A, Reinstrup P, Ryding E, et al. Effects of iso- and hypervolemic hemodilution on regional cerebral blood flow and oxygen delivery for patients with vasospasm after aneurysmal subarachnoid hemorrhage. *Acta Neurochir (Wien)*. 2002;144:703-712; discussion 12-13.
37. Kassell NF, Peerless SJ, Durward QJ, Beck DW, Drake CG, Adams HP. Treatment of ischemic deficits from vasospasm

- with intravascular volume expansion and induced arterial hypertension. *Neurosurgery*. 1982;11:337-343.
38. Otsubo H, Takemae T, Inoue T, Kobayashi S, Sugita K. Normovolaemic induced hypertension therapy for cerebral vasospasm after subarachnoid haemorrhage. *Acta Neurochir (Wien)*. 1990;103:18-26.
39. Darby JM, Yonas H, Marks EC, Durham S, Snyder RW, Nemoto EM. Acute cerebral blood flow response to dopamine-induced hypertension after subarachnoid hemorrhage. *J Neurosurg*. 1994;80:857-864.
40. Kosnik EJ, Hunt WE. Postoperative hypertension in the management of patients with intracranial arterial aneurysms. *J Neurosurg*. 1976;45:148-154.
41. Miller JA, Dacey RG, Jr., Diringer MN. Safety of hypertensive hypervolemic therapy with phenylephrine in the treatment of delayed ischemic deficits after subarachnoid hemorrhage. *Stroke*. 1995;26:2260-2266.
42. Muehlschlegel S, Dunser MW, Gabrielli A, Wenzel V, Layon AJ. Arginine vasopressin as a supplementary vasopressor in refractory hypertensive, hypervolemic, hemodilutional therapy in subarachnoid hemorrhage. *Neurocrit Care*. 2007;6:3-10.
43. Rondeau N, Cinotti R, Rozec B, et al. Dobutamine-induced high cardiac index did not prevent vasospasm in subarachnoid hemorrhage patients: A randomized controlled pilot study. *Neurocrit Care*. 2012;17:183-190.
44. Levy ML, Rabb CH, Zelman V, Giannotta SL. Cardiac performance enhancement from dobutamine in patients refractory to hypervolemic therapy for cerebral vasospasm. *J Neurosurg*. 1993;79:494-499.
45. Hayashida N, Tomoeda H, Oda T, et al. Inhibitory effect of milrinone on cytokine production after cardiopulmonary bypass. *Ann Thorac Surg*. 1999;68:1661-1667.
46. Lannes M, Teitelbaum J, del Pilar Cortes M, Cardoso M, Angle M. Milrinone and homeostasis to treat cerebral vasospasm associated with subarachnoid hemorrhage: The Montreal Neurological Hospital protocol. *Neurocrit Care*. 2012;16:354-362.
47. Yoneda H, Nakamura T, Shirao S, et al. Multicenter prospective cohort study on volume management after subarachnoid hemorrhage: Hemodynamic changes according to severity of subarachnoid hemorrhage and cerebral vasospasm. *Stroke*. 2013;44:2155-2161.
48. Athar MK, Levine JM. Treatment options for cerebral vasospasm in aneurysmal subarachnoid hemorrhage. *Neurotherapeutics*. 2012;9:37-43.
49. Kazda S, Towart R. Nimodipine: A new calcium antagonistic drug with a preferential cerebrovascular action. *Acta Neurochir (Wien)*. 1982;63:259-265.
50. Harris RJ, Branston NM, Symon L, Bayhan M, Watson A. The effects of a calcium antagonist, nimodipine, upon physiological responses of the cerebral vasculature and its possible influence upon focal cerebral ischaemia. *Stroke*. 1982;13:759-766.
51. Allen GS, Ahn HS, Preziosi TJ, et al. Cerebral arterial spasm—a controlled trial of nimodipine in patients with subarachnoid hemorrhage. *N Engl J Med*. 1983;308:619-624.
52. Choi HA, Ko SB, Chen H, et al. Acute effects of nimodipine on cerebral vasculature and brain metabolism in high grade subarachnoid hemorrhage patients. *Neurocrit Care*. 2012;16:363-367.
53. Dorhout Mees SM, Rinkel GJ, Feigin VL, et al. Calcium antagonists for aneurysmal subarachnoid haemorrhage. *Cochrane Database Syst Rev*. 2007;CD000277.
54. Dorhout Mees SM, Rinkel GJ, Feigin VL, et al. Calcium antagonists for aneurysmal subarachnoid hemorrhage. *Stroke*. 2008;39:514-515.
55. Pickard JD, Murray GD, Illingworth R, et al. Effect of oral nimodipine on cerebral infarction and outcome after subarachnoid haemorrhage: British Aneurysm Nimodipine Trial. *Br Med J*. 1989;298:636-642.
56. Philippon J, Grob R, Dagreou F, Guggiari M, Rivierez M, Viars P. Prevention of vasospasm in subarachnoid haemorrhage. A controlled study with nimodipine. *Acta Neurochir (Wien)*. 1986;82:110-114.
57. Petruk KC, West M, Mohr G, et al. Nimodipine treatment in poor-grade aneurysm patients. Results of a multicenter double-blind placebo-controlled trial. *J Neurosurg*. 1988;68:505-517.
58. Jan M, Buchheit F, Tremoulet M. Therapeutic trial of intravenous nimodipine in patients with established cerebral vasospasm after rupture of intracranial aneurysms. *Neurosurgery*. 1988;23:154-157.
59. Karinen P, Koivukangas P, Ohinmaa A, Koivukangas J, Ohman J. Cost-effectiveness analysis of nimodipine treatment after aneurysmal subarachnoid hemorrhage and surgery. *Neurosurgery*. 1999;45:780-784; discussion 4-5.
60. Messeter K, Brandt L, Ljunggren B, et al. Prediction and prevention of delayed ischemic dysfunction after aneurysmal subarachnoid hemorrhage and early operation. *Neurosurgery*. 1987;20:548-553.
61. Neil-Dwyer G, Mee E, Dorrance D, Lowe D. Early intervention with nimodipine in subarachnoid haemorrhage. *Eur Heart J*. 1987;8(Suppl K):41-47.
62. Mee E, Dorrance D, Lowe D, Neil-Dwyer G. Controlled study of nimodipine in aneurysm patients treated early after subarachnoid hemorrhage. *Neurosurgery*. 1988;22:484-491.
63. Ohman J, Servo A, Heiskanen O. Long-term effects of nimodipine on cerebral infarcts and outcome after aneurysmal subarachnoid hemorrhage and surgery. *J Neurosurg*. 1991;74:8-13.
64. Haley EC Jr, Kassell NF, Torner JC. A randomized controlled trial of high-dose intravenous nicardipine in aneurysmal subarachnoid hemorrhage. A report of the Cooperative Aneurysm Study. *J Neurosurg*. 1993;78:537-547.
65. Haley EC Jr, Kassell NF, Torner JC, Truskowski LL, German TP. A randomized trial of two doses of nicardipine in

- aneurysmal subarachnoid hemorrhage. A report of the Cooperative Aneurysm Study. *J Neurosurg.* 1994;80:788-796.
66. van den Bergh WM, Algra A, van der Sprenkel JW, Tulleken CA, Rinkel GJ. Hypomagnesemia after aneurysmal subarachnoid hemorrhage. *Neurosurgery.* 2003;52:276-281; discussion 81-82.
 67. Taccone FS. Vasodilation and neuroprotection: The magnesium saga in subarachnoid hemorrhage. *Crit Care Med.* 2010;38:1382-1384.
 68. van den Bergh WM, Dijkhuizen RM, Rinkel GJ. Potentials of magnesium treatment in subarachnoid haemorrhage. *Magnes Res.* 2004;17:301-313.
 69. Muroi C, Terzic A, Fortunati M, Yonekawa Y, Keller E. Magnesium sulfate in the management of patients with aneurysmal subarachnoid hemorrhage: A randomized, placebo-controlled, dose-adapted trial. *Surg Neurol.* 2008;69:33-39; discussion 9.
 70. van den Bergh WM, Algra A, van Kooten F, et al. Magnesium sulfate in aneurysmal subarachnoid hemorrhage: A randomized controlled trial. *Stroke.* 2005;36:1011-1015.
 71. Veyna RS, Seyfried D, Burke DG, et al. Magnesium sulfate therapy after aneurysmal subarachnoid hemorrhage. *J Neurosurg.* 2002;96:510-514.
 72. Wong GK, Boet R, Poon WS, et al. Intravenous magnesium sulphate for aneurysmal subarachnoid hemorrhage: An updated systemic review and meta-analysis. *Crit Care.* 2011;15:R52.
 73. Wong GK, Poon WS, Chan MT, et al. Intravenous magnesium sulphate for aneurysmal subarachnoid hemorrhage (IMASH): A randomized, double-blinded, placebo-controlled, multicenter phase III trial. *Stroke.* 2010;41:921-926.
 74. Westermaier T, Stetter C, Vince GH, et al. Prophylactic intravenous magnesium sulfate for treatment of aneurysmal subarachnoid hemorrhage: A randomized, placebo-controlled, clinical study. *Crit Care Med.* 2010;38:1284-1290.
 75. Bradford CM, Finfer S, O'Connor A, et al. A randomised controlled trial of induced hypermagnesaemia following aneurysmal subarachnoid haemorrhage. *Crit Care Resusc.* 2013;15:119-125.
 76. Pluta RM. Delayed cerebral vasospasm and nitric oxide: Review, new hypothesis, and proposed treatment. *Pharmacol Ther.* 2005;105:23-56.
 77. Muroi C, Seule M, Mishima K, Keller E. Novel treatments for vasospasm after subarachnoid hemorrhage. *Curr Opin Crit Care.* 2012;18:119-126.
 78. Dhar R, Diringer M. Statins and anti-inflammatory therapies for subarachnoid hemorrhage. *Curr Treat Options Neurol.* 2012;14:164-174.
 79. Sillberg VA, Wells GA, Perry JJ. Do statins improve outcomes and reduce the incidence of vasospasm after aneurysmal subarachnoid hemorrhage: A meta-analysis. *Stroke.* 2008;39:2622-2626.
 80. Chou SH, Smith EE, Badjatia N, et al. A randomized, double-blind, placebo-controlled pilot study of simvastatin in aneurysmal subarachnoid hemorrhage. *Stroke.* 2008;39:2891-2893.
 81. Lynch JR, Wang H, McGirt MJ, et al. Simvastatin reduces vasospasm after aneurysmal subarachnoid hemorrhage: Results of a pilot randomized clinical trial. *Stroke.* 2005;36:2024-2026.
 82. Tseng MY, Czosnyka M, Richards H, Pickard JD, Kirkpatrick PJ. Effects of acute treatment with pravastatin on cerebral vasospasm, autoregulation, and delayed ischemic deficits after aneurysmal subarachnoid hemorrhage: A phase II randomized placebo-controlled trial. *Stroke.* 2005;36:1627-1632.
 83. Vergouwen MD, Meijers JC, Geskus RB, et al. Biologic effects of simvastatin in patients with aneurysmal subarachnoid hemorrhage: A double-blind, placebo-controlled randomized trial. *J Cereb Blood Flow Metab.* 2009;29:1444-1453.
 84. Sanchez-Pena P, Nouet A, Clarencon F, et al. Atorvastatin decreases computed tomography and S100-assessed brain ischemia after subarachnoid aneurysmal hemorrhage: A comparative study. *Crit Care Med.* 2012;40:594-602.
 85. Garg K, Sinha S, Kale SS, et al. Role of simvastatin in prevention of vasospasm and improving functional outcome after aneurysmal sub-arachnoid hemorrhage: A prospective, randomized, double-blind, placebo-controlled pilot trial. *Br J Neurosurg.* 2013;27:181-186.
 86. Macdonald RL, Kassell NF, Mayer S, et al. Clazosentan to overcome neurological ischemia and infarction occurring after subarachnoid hemorrhage (CONSCIOUS-1): Randomized, double-blind, placebo-controlled phase 2 dose-finding trial. *Stroke.* 2008;39:3015-3021.
 87. Macdonald RL, Higashida RT, Keller E, et al. Clazosentan, an endothelin receptor antagonist, in patients with aneurysmal subarachnoid haemorrhage undergoing surgical clipping: A randomised, double-blind, placebo-controlled phase 3 trial (CONSCIOUS-2). *Lancet Neurol.* 2011;10:618-625.
 88. Macdonald RL, Higashida RT, Keller E, et al. Preventing vasospasm improves outcome after aneurysmal subarachnoid hemorrhage: Rationale and design of CONSCIOUS-2 and CONSCIOUS-3 trials. *Neurocrit Care.* 2010;13:416-424.
 89. Vergouwen MD, Algra A, Rinkel GJ. Endothelin receptor antagonists for aneurysmal subarachnoid hemorrhage: A systematic review and meta-analysis update. *Stroke.* 2012;43:2671-2676.
 90. Macdonald RL, Higashida RT, Keller E, et al. Randomized trial of clazosentan in patients with aneurysmal subarachnoid hemorrhage undergoing endovascular coiling. *Stroke.* 2012;43:1463-1469.
 91. Haley EC, Jr., Kassell NF, Alves WM, Weir BK, Hansen CA. Phase II trial of tirilazad in aneurysmal subarachnoid hemorrhage. A report of the Cooperative Aneurysm Study. *J Neurosurg.* 1995;82:786-790.

92. Kassell NF, Haley EC, Jr., Apperson-Hansen C, Alves WM. Randomized, double-blind, vehicle-controlled trial of tirilazad mesylate in patients with aneurysmal subarachnoid hemorrhage: A cooperative study in Europe, Australia, and New Zealand. *J Neurosurg.* 1996;84:221-228.
93. Haley EC, Jr., Kassell NF, Apperson-Hansen C, Maile MH, Alves WM. A randomized, double-blind, vehicle-controlled trial of tirilazad mesylate in patients with aneurysmal subarachnoid hemorrhage: A cooperative study in North America. *J Neurosurg.* 1997;86:467-474.
94. Lanzino G, Kassell NF. Double-blind, randomized, vehicle-controlled study of high-dose tirilazad mesylate in women with aneurysmal subarachnoid hemorrhage. Part II. A cooperative study in North America. *J Neurosurg.* 1999;90:1018-1024.
95. Lanzino G, Kassell NF, Dorsch NW, et al. Double-blind, randomized, vehicle-controlled study of high-dose tirilazad mesylate in women with aneurysmal subarachnoid hemorrhage. Part I. A cooperative study in Europe, Australia, New Zealand, and South Africa. *J Neurosurg.* 1999;90:1011-1017.
96. Glick H, Willke R, Polsky D, et al. Economic analysis of tirilazad mesylate for aneurysmal subarachnoid hemorrhage. Economic evaluation of a phase III clinical trial in Europe and Australia. *Int J Technol Assess Health Care.* 1998;14:145-160.
97. Senbokuya N, Kinouchi H, Kanemaru K, et al. Effects of cilostazol on cerebral vasospasm after aneurysmal subarachnoid hemorrhage: A multicenter prospective, randomized, open-label blinded end point trial. *J Neurosurg.* 2013;118:121-130.
98. Shirao S, Fujisawa H, Kudo A, et al. Inhibitory effects of eicosapentaenoic acid on chronic cerebral vasospasm after subarachnoid hemorrhage: Possible involvement of a sphingomyelinase-phosphorylcholine-rho-kinase pathway. *Cerebrovasc Dis.* 2008;26:30-37.
99. Yoneda H, Shirao S, Nakagawara J, Ogasawara K, Tomimaga T, Suzuki M. A prospective, multi-center, randomized study of the efficacy of eicosapentaenoic acid for cerebral vasospasm: The EVAS Study. *World Neurosurg.* 2014;81(2):309-315.
100. Weant KA, Ramsey CN 3rd, Cook AM. Role of intra-arterial therapy for cerebral vasospasm secondary to aneurysmal subarachnoid hemorrhage. *Pharmacotherapy.* 2010;30:405-417.
101. Kassell NF, Helm G, Simmons N, Phillips CD, Cail WS. Treatment of cerebral vasospasm with intra-arterial papaverine. *J Neurosurg.* 1992;77:848-852.
102. Firlik KS, Kaufmann AM, Firlik AD, Jungreis CA, Yonas H. Intra-arterial papaverine for the treatment of cerebral vasospasm following aneurysmal subarachnoid hemorrhage. *Surg Neurol.* 1999;51:66-74.
103. Clouston JE, Numaguchi Y, Zoarski GH, Aldrich EF, Simard JM, Zitnay KM. Intraarterial papaverine infusion for cerebral vasospasm after subarachnoid hemorrhage. *Am J Neuroradiol.* 1995;16:27-38.
104. Liu JK, Tenner MS, Gottfried ON, et al. Efficacy of multiple intraarterial papaverine infusions for improvement in cerebral circulation time in patients with recurrent cerebral vasospasm. *J Neurosurg.* 2004;100:414-421.
105. Little N, Morgan MK, Grinnell V, Sorby W. Intra-arterial papaverine in the management of cerebral vasospasm following subarachnoid haemorrhage. *J Clin Neurosci.* 1994;1:42-46.
106. Morgan M, Halcrow S, Sorby W, Grinnell V. Outcome of aneurysmal subarachnoid haemorrhage following the introduction of papaverine angioplasty. *J Clin Neurosci.* 1996;3:139-142.
107. Numaguchi Y, Zoarski GH. Intra-arterial papaverine treatment for cerebral vasospasm: Our experience and review of the literature. *Neurol Med Chir (Tokyo).* 1998;38:189-195.
108. Cross DT 3rd, Moran CJ, Angtuaco EE, Milburn JM, Diringner MN, Dacey RG Jr. Intracranial pressure monitoring during intraarterial papaverine infusion for cerebral vasospasm. *Am J Neuroradiol.* 1998;19:1319-1323.
109. Milburn JM, Moran CJ, Cross DT 3rd, Diringner MN, Pilgram TK, Dacey RG Jr. Increase in diameters of vasospastic intracranial arteries by intraarterial papaverine administration. *J Neurosurg.* 1998;88:38-42.
110. Polin RS, Hansen CA, German P, Chaddock JB, Kassell NF. Intra-arterially administered papaverine for the treatment of symptomatic cerebral vasospasm. *Neurosurgery.* 1998;42:1256-1264; discussion 64-67.
111. Kerz T, Boor S, Beyer C, Welschehold S, Schuessler A, Oertel J. Effect of intraarterial papaverine or nimodipine on vessel diameter in patients with cerebral vasospasm after subarachnoid hemorrhage. *Br J Neurosurg.* 2012;26:517-524.
112. Carhuapoma JR, Qureshi AI, Tamargo RJ, Mathis JM, Hanley DF. Intra-arterial papaverine-induced seizures: Case report and review of the literature. *Surg Neurol.* 2001;56:159-163.
113. Smith WS, Dowd CF, Johnston SC, et al. Neurotoxicity of intra-arterial papaverine preserved with chlorobutanol used for the treatment of cerebral vasospasm after aneurysmal subarachnoid hemorrhage. *Stroke.* 2004;35:2518-2522.
114. Badjatia N, Topcuoglu MA, Pryor JC, et al. Preliminary experience with intra-arterial nicardipine as a treatment for cerebral vasospasm. *Am J Neuroradiol.* 2004;25:819-826.
115. Linfante I, Delgado-Mederos R, Andreone V, Gounis M, Hendricks L, Wakhloo AK. Angiographic and hemodynamic effect of high concentration of intra-arterial nicardipine in cerebral vasospasm. *Neurosurgery.* 2008;63:1080-1086; discussion 6-7.
116. Tejada JG, Taylor RA, Ugurel MS, Hayakawa M, Lee SK, Chaloupka JC. Safety and feasibility of intra-arterial nicardipine for the treatment of subarachnoid hemorrhage-associated vasospasm: Initial clinical experience with high-dose infusions. *Am J Neuroradiol.* 2007;28:844-848.

117. Ehtisham A, Taylor S, Bayless L, Samuels OB, Klein MW, Janzen JM. Use of intrathecal nicardipine for aneurysmal subarachnoid hemorrhage-induced cerebral vasospasm. *South Med J*. 2009;102:150-153.
118. Goodson K, Lapointe M, Monroe T, Chalela JA. Intraventricular nicardipine for refractory cerebral vasospasm after subarachnoid hemorrhage. *Neurocrit Care*. 2008;8:247-252.
119. Barth M, Capelle HH, Weidauer S, et al. Effect of nicardipine prolonged-release implants on cerebral vasospasm and clinical outcome after severe aneurysmal subarachnoid hemorrhage: A prospective, randomized, double-blind phase IIa study. *Stroke*. 2007;38:330-336.
120. Albanese E, Russo A, Quiroga M, Willis RN, Jr., Mericle RA, Ulm AJ. Ultrahigh-dose intraarterial infusion of verapamil through an indwelling microcatheter for medically refractory severe vasospasm: Initial experience. *J Neurosurg*. 2010;113:913-922.
121. Feng L, Fitzsimmons BF, Young WL, et al. Intraarterially administered verapamil as adjunct therapy for cerebral vasospasm: Safety and 2-year experience. *Am J Neuroradiol*. 2002;23:1284-1290.
122. Keuskamp J, Murali R, Chao KH. High-dose intraarterial verapamil in the treatment of cerebral vasospasm after aneurysmal subarachnoid hemorrhage. *J Neurosurg*. 2008;108:458-463.
123. Flexman AM, Ryerson CJ, Talke PO. Hemodynamic stability after intraarterial injection of verapamil for cerebral vasospasm. *Anesth Analg*. 2012;114:1292-1296.
124. Agrawal A, Patir R, Kato Y, Chopra S, Sano H, Kanno T. Role of intraventricular sodium nitroprusside in vasospasm secondary to aneurysmal subarachnoid haemorrhage: A 5-year prospective study with review of the literature. *Minim Invasive Neurosurg*. 2009;52:5-8.
125. Arakawa Y, Kikuta K, Hojo M, Goto Y, Ishii A, Yamagata S. Milrinone for the treatment of cerebral vasospasm after subarachnoid hemorrhage: Report of seven cases. *Neurosurgery*. 2001;48:723-728; discussion 8-30.
126. Schmidt U, Bittner E, Pivi S, Marota JJ. Hemodynamic management and outcome of patients treated for cerebral vasospasm with intraarterial nicardipine and/or milrinone. *Anesth Analg*. 2010;110:895-902.
127. Fraticelli AT, Cholley BP, Losser MR, Saint Maurice JP, Payen D. Milrinone for the treatment of cerebral vasospasm after aneurysmal subarachnoid hemorrhage. *Stroke*. 2008;39:893-898.
128. Arakawa Y, Kikuta K, Hojo M, et al. Milrinone reduces cerebral vasospasm after subarachnoid hemorrhage of WFNS grade IV or V. *Neurol Med Chir (Tokyo)*. 2004;44:393-400; discussion 1.
129. Findlay JM, Kassell NF, Weir BK, et al. A randomized trial of intraoperative, intracisternal tissue plasminogen activator for the prevention of vasospasm. *Neurosurgery*. 1995;37:168-176; discussion 77-78.
130. Hamada J, Kai Y, Morioka M, et al. Effect on cerebral vasospasm of coil embolization followed by microcatheter intrathecal urokinase infusion into the cisterna magna: A prospective randomized study. *Stroke*. 2003;34:2549-2554.
131. Li YH, Guo K, Zi XH, Song Z. [Combining exchange of cerebrospinal fluid with small dose of urokinase injection for subarachnoid hemorrhage]. *Zhong Nan Da Xue Xue Bao Yi Xue Ban*. 2005;30:217-220.
132. Hanggi D, Eicker S, Beseoglu K, Behr J, Turowski B, Steiger HJ. A multimodal concept in patients after severe aneurysmal subarachnoid hemorrhage: Results of a controlled single centre prospective randomized multimodal phase I/II trial on cerebral vasospasm. *Cent Eur Neurosurg*. 2009;70:61-67.
133. Kramer AH, Fletcher JJ. Locally-administered intrathecal thrombolytics following aneurysmal subarachnoid hemorrhage: A systematic review and meta-analysis. *Neurocrit Care*. 2011;14:489-499.
134. Ducruet AF, Hickman ZL, Zacharia BE, et al. Exacerbation of perihematoma edema and sterile meningitis with intraventricular administration of tissue plasminogen activator in patients with intracerebral hemorrhage. *Neurosurgery*. 2010;66:648-655.
135. Eicker SO, Beseoglu K, Etminan N, et al. The effect of intraventricular thrombolysis in combination with low-frequency head motion after severe subarachnoid hemorrhage: Interim analysis of safety, clot clearance rate and delayed cerebral ischemia. *Acta Neurochir Suppl*. 2012;114:323-328.
136. Etminan N, Beseoglu K, Eicker SO, Turowski B, Steiger HJ, Hanggi D. Prospective, randomized, open-label phase II trial on concomitant intraventricular fibrinolysis and low-frequency rotation after severe subarachnoid hemorrhage. *Stroke*. 2013;44:2162-2168.
137. Velat GJ, Kimball MM, Mocco JD, Hoh BL. Vasospasm after aneurysmal subarachnoid hemorrhage: Review of randomized controlled trials and meta-analyses in the literature. *World Neurosurg*. 2011;76:446-454. ■